514 Rec'd PCT/PTO 13 MAY 1999

FORM PTO-1390 (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
30394-1027	09/308150

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/NL97/00624	14 November 1997	15 November 1996

TITLE OF INVENTION PEPTIDE DERIVED FROM AN ANTIGEN RECOGNIZED BY AUTOANTIBODIES FROM PATIENTS WITH RHEUMATOID ARTHRITIS, ANTIBODY DIRECTED AGAINST SAID PEPTIDE, A COMBINATORIAL ANTIGEN, AND A METHOD OF DETECTING AUTO-IMMUNE ANTIBODIES

APPLICANT(S) FOR DO/EO/US Waltherus Jacobus Wilhelmus Van Venrooij, Gerardus Antonius Schellekens, Jozef Maria Hendrik Raats, Rene Michael Antonius Hoet

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (~~required only if~~ in the event it was not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). (unsigned)
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: Associate Power of Attorney

514 Rec'd PCT/PTO 13 MAY 1999

U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 09/308150	INTERNATIONAL APPLICATION NO. PCT/NL97/00624	ATTORNEY'S DOCKET NUMBER 30394-1027

17. [X] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $970.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $840.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $760.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) $670.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $96.00

	CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	15 - 20 =	--	X $18.00	$	
Independent claims	1 - 3 =	--	X $78.00	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00		

TOTAL OF ABOVE CALCULATIONS =	$ 840.00	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).	$	
SUBTOTAL =	$ 840.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +	$	
TOTAL NATIONAL FEE =	$ 840.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +	$	
TOTAL FEES ENCLOSED =	$ 840.00	
	Amount to be: refunded	$
	charged	$

a. [X] A check in the amount of $ 840.00 to cover the above fees is enclosed

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-4213. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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(Transmittal Letter to the United States Designated Office (DO/US) ...

Peptide derived from an antigen recognized by autoantibodies from patients with rheumatoid arthritis, antibody directed against said peptide, a combinatorial antigen, and a method of detecting auto-immune antibodies

The present invention relates to a peptide derived from an antigen recognized by autoantibodies from patients with rheumatoid arthritis, which peptide is reactive with autoimmune antibodies from a patient suffering from rheumatoid arthritis.

Such a peptide is known from the European patent application 0 511 116 (Clonatec S.A.). This application describes an antigen comprising a filaggrin or profilaggrin fragment. The peptide is recognized by rheumatoid arthritis-specific autoimmune antibodies. Rheumatoid arthritis (RA) is a systemic autoimmune disease. It is the most commonly occurring inflammatory disease of the joints. It is chronic and may lead to severe physical disablement.

The object of the present is to provide a peptide which is reactive with autoimmune antibodies from a patient suffering from rheumatoid arthritis, which peptide is suitable for diagnostic research with increased specificity while also being useful for other purposes such as obtaining (raising, selecting and isolating) poly- and monoclonal antibodies.

To this end the peptide according to the invention is characterized in that the derived peptide that is reactive with autoimmune antibodies, corresponds to a part of a mRNA molecule coding for the antigen, said part comprising a codon for an arginine residue, and the arginine residue in the derived peptide, which is reactive with autoimmune antibodies, is a modified arginine residue.

Surprisingly, the peptide according to the invention that possesses a modified arginine residue, proved to be very suitable for the specific diagnosis of rheumatoid arthritis.

To this day, no specific serological test is available for RA. The only test frequently employed is based on the determination of rheumatoid factors (RF; Ref. 1) which are found in 70% of the RA patients. However, this test is not very specific and is characterized by a relatively large number of false positives. For patients suffering from systemic lupus erythematosus the percentage of false positives is approximately 20% and for healthy individuals approximately 5%.

Preferably the peptide is characterized in that the modified arginine residue's side chain is a side chain according to Formula I on the formula sheet, in which

X = NH_2, CH_3, $NHCH_3$ or $N(CH_3)_2$;

Y = O, NH, $NHCH_3$ or $N(CH_3)_2$;

Z = O, NH or CH_2; and

n = 2, 3 or 4, on the condition that when X = NH_2 and Z = NH, Y is not NH; and the modified arginine residue is in particular a citrulline residue. For citrulline, X = NH_2, Y = O, Z = NH and n = 3.

A preferred peptide is the peptide selected from the group of peptides having the Formula II - X on the formula sheet.

By using the peptide according to Formula II, it is possible to establish the presence of rheumatoid arthritis in about 36% of patients actually suffering from rheumatoid arthritis, while the percentage of false positives for other autoimmune diseases and healthy individuals is less than 2%.

According to a favourable embodiment the peptide is a cyclic peptide, for instance, due to the presence of a cystine residue.

In some cases such a cyclic peptide exhibits an increased immunological affinity.

The preferred cyclic peptide is the peptide having the Formula XI on the formula sheet.

Preferably the peptide is a synthetic peptide.

The reactive peptide according to the invention can be obtained pure and in large quantities by means of

organic synthesis, making immunological testing on a large scale possible.

According to an alternative embodiment, the peptide in accordance with the invention is characterized in that the peptide is obtained by the proteolytic treatment of (pro)filaggrin, separation of peptide fragments formed by proteolysis and subsequent selection on the presence of a modified arginine residue in a peptide which was formed during the proteolytic treatment.

In this manner peptides can be identified which can increase the sensitivity of a rheumatoid arthritis test. The term sensitivity is in the present application to be understood to mean the ability of a test to properly identify a patient suffering from rheumatoid arthritis.

According to a favourable embodiment, the antigen is (pro)filaggrin, and the peptide is reactive with a rheumatoid arthritis patient's autoimmune antibodies which are reactive with (pro)filaggrin.

The peptide has been shown to be very suitable for high-specificity testing (few false positives) for rheumatism.

The present invention also relates to an antibody which is cross-reactive with an antibody raised against a peptide according to the invention.

Such an antibody is useful for the indication of rheumatoid arthritis by analysing sections of biopsy samples and immunological tests of the sandwich type.

The antibody is preferably a monoclonal antibody.

According to another preferred embodiment, the antibody is obtained by using as antigen a peptide in accordance with the invention.

A suitable antibody according to the invention is characterized in that it is cross reactive with the antibody as produced by Escherichia coli TG1 with plasmid RA3, deposited at the Centraalbureau voor Schimmelcultures, at Baarn, the Netherlands under accession number CBS143.96.

The invention further relates to an organic compound comprising a part that is able to compete with a peptide according to one of the claims 1 to 9 for binding

to an antibody which is specific for said peptide, wherein at least said part of the organic compound can be prepared by means of combinationary chemistry.

Such organic compounds are found by competitive selection wherein a peptide of the invention competes for recognition by an antibody of the invention, such as the antibody produced by E. coli CBS143.96. The organic compounds, which are often cheaper to produce than antigens that are prepared solely on the basis of amino acids that may or may not comprise side chains, are suitable for immunological kits for diagnosing RA. Also, after coupling to a solid carrier, said organic compounds could be applied to lower, through adsorption, the level of autoimmune antibodies in the blood of patients suffering from RA.

Finally, the invention relates to a method of detecting autoimmune antibodies against rheumatoid arthritis.

The method according to the invention is characterized in that in an immunological test at least one immunologically active molecule selected from the group consisting of i) a peptide according to the invention; ii) a recombinatory organic molecule according to the invention; and iii) an antibody according to the invention is used.

In addition to increased sensitivity other advantages are achieved, in particular better reproducibility, quantitative information and better applicability for prognostic purposes.

To a person skilled in the art it will be apparent that there are a number of possible variations to the present invention as specified by the appended claims. For instance, the peptides mentioned on the formula sheet may also be part of other oligopeptides. They may be provided at one or both ends with one or more other amino acids while also, two or more peptides according to the invention may be part of one oligopeptide. It is also possible to shorten the peptides by one or more amino acids, provided this does not have a significantly adverse effect on

the reactivity. The expert is familiar with the manner in which peptides and organic compounds according to the invention may optionally be labelled or be coupled to a carrier, and how on the basis of such antigens an immunological test may be developed, using the standard techniques well-known in the field.

The invention will now be explained in more detail by means of the following example.

Materials and methods

Peptide synthesis: Peptides were selected for synthesis on the basis of amino acid sequences derived from known cDNA sequences of human profilaggrin (Ref. 2; Ref. 3). The peptides were synthesized on solid phase using the method described by Schellekens et al. (Ref. 4). The peptides were at least 95% pure, as determined by the elution profile by means of reversed phase chromatography and the relative absorption at 214 nm. The composition of the peptides was confirmed by means of mass spectrometry (MALDI-MS). All peptides were synthesized as peptide amides.

TABLE 1

Synthesized peptides

The peptide names starting with "cf" are based on the C-terminal end (amino acids 306-324); and the peptide names staring with "nf" are based on the sequence near the N-terminal end (amino acids 18 32 for nfc1).
Amino acid sequences based on cDNA of a profilaggrin repeat.

Name	Peptide sequence*
cfc1	S H Q E S T X G R S R G R S G R S G S
cfc2	S H Q E S T R G X S R G R S G R S G S
cfc3	S H Q E S T R G R S X G R S G R S G S
cfc4	S H Q E S T R G R S R G X S G R S G S
cfc5	S H Q E S T R G R S R G R S G X S G S
cfc6	S H Q E S T X G X S R G R S G R S G S
cfc7	S H Q E S T X G R S X G R S G R S G S
cfc8	S H Q E S T X G R S R G X S G R S G S
cfc9	S H Q E S T X G R S R G R S G X S G S
cf	S H Q E S T R G R S R G R S G R S G S
cfA	S H Q E S T A G R S R G R S G R S G S
cfE	S H Q E S T E G R S R G R S G R S G S
cfQ	S H Q E S T Q G R S R G R S G R S G S
nfc1	T G P S T R G R Q G S X H E
nf	E S S H G W T G P S T R G R Q G S R H E

* (A = alanine; G = glycine; H = histidine; E = glutamic acid; P = proline; R = arginine; Q = glutamine; S = serine; T = threonine; W = tryptophan; X = citrulline)

Detection by means of ELISA

Via an N-oxysuccinimide surface the peptides were covalently coupled to the wells of 96-well microtitre plates (Costar amide binding plates) in an amount of 1 µg/well. Coupling took place for 16 hours at 4EC and pH 9.0. The plates were blocked for 1 hour with 2% bovine serum albumin. The sera were diluted 200 times in a diluent (0.3% BSA, 350 mM NaCl, 10 mM Tris-HCl pH 7.6, 1% vol./vol. Triton X-100, 0.5% w./vol. Na-deoxycholate, 0.1% SDS) supplemented with 10% normal rabbit serum, and incubated for one hour at room temperature. After washing the plates (3 times with PBS containing 0.05% by vol. of Tween®20), 100 µl of antihuman IgG conjugated with peroxidase (Dako P214), 1000 times diluted in dilution buffer, was added to the wells. After incubation for 1 hour at room temperature, the plates were washed 3 times with PBS/Tween®, and bound antibodies were detected with tetramethyl benzidine as a substrate. After 10 minutes the reaction was stopped by adding 100 µl of 2 M sulphuric acid per well. Readout occurred at 450 nm. Sera having an OD_{450} of 0.2, after deduction of the blank for the respective serum (a well without a coupled peptide), were considered to be positive.

Results

The results are listed in Table 2. In total, 288 sera from patients suffering from rheumatoid diseases were used, 132 of which were from patients suffering from rheumatoid arthritis.

TABLE 2

Results with peptide cfc1 to cfc9 (Formula II to X of the formula sheet)

Peptide*	RA sera (%) (n = 134)	control sera[1] (%) (n = 154)	SLE[2] (%) (n = 50)	SSC[3] (%) (n = 50)	pSS[4] (%) (n = 50)	PM/DM[5] (%) (n = 50)
cfc1	49 (36)	1 (0.6)	1 (2)	0	0	0
cfc2	27 (20)	4 (2.6)	1 (2)	0	1 (2)	1 (2)
cfc3	37(28)	2 (0.6)	0	0	1 (2)	1 (2)
cfc4	32 (24)	2 (1.3)	0	0	0	0
cfc5	64 (48)	1 (0.6)	0	1 (2)	2 (4)	1 (2)
cfc6	65 (48)	1 (0.6)	0	0	2 (4)	1 (2)
cfc7	60 (45)	1 (0.6)	0	0	1 (2)	1 (2)
cfc8	55 (41)	1 (0.6)	0	0	1 (2)	1 (2)
cfc9	57 (42)	1 (0.6)	0	0	2 (4)	0

[1]) Control sera are from patients suffering from rheumatic diseases other than RA.

[2]) SLE is systemic lupus erythematosus.

[3]) pSS is primary Sjögren's syndrome.

[4]) SSC is systemic scleroderma.

[5]) PM/DM is polymyositis/dermatomyositis.

Of the total of 134 RA sera from patients suffering from rheumatoid arthritis, 102 were positive with at least one peptide from the cfc1 to cfc9 series. Therefore, when using these peptides, the sensitivity was 76% (102/134). Of the total of 354 control sera, 13 sera were positive on at least one peptide from the cfc1 to cfc9 series. Therefore the test sensitivity, expressed as percentage of true

positives, was 96%. Of the 37 sera that were reactive with cfc3, none were not recognized by peptide cfc1 or cfc23. Of the sera that were reactive with cfc7, cfc8 and cfc9, none were not recognized by cfc1, cfc2, cfc4, cfc5 or cfc6. This means that cfc2, cfc7, cfc8 and cfc9 do not contribute to the test sensitivity and a test sensitivity of 76% may be realized by using the combination of the peptides cfc1, cfc2, cfc4, cfc5 and cfc6.

It should be noted that these percentages depend on the specificity-threshold value applied by applicants. The same data (from the ELISA experiments) can be interpreted as a sensitivity of approximately 80-85% by choosing a slightly lower sensitivity, which incidentally, is still much better than the one obtainable when using the known rheumatoid factor test (Ref. 1).

Sera from patients suffering from various infectious diseases (Borrelia, syphilis, malaria, endocarditis, Legionella, tuberculosis, mycoplasma, Yersinia, salmonella, parvovirus B19, Epstein-Barr virus, rubella, schistosomiasis, Toxoplasma, leishmaniasis, Chagas' disease) were tested for the presence of antibodies reactive with cfc1. Of the 308 tested sera 9 were positive. This means that the specificity was 97%, a considerable improvement compared with the RF test.

Variants of cfc1 wherein citrulline was replaced by a neutral (alanine; cfA), acid (glutamic acid; cfE) or amide (glutamine; cfQ) residue, did not seem to be immunologically reactive. The same applies to the control peptide cf, which does not possess a modified arginine residue.

With the aid of the above-described ELISA, a cyclic variant (with the Formula XI on the formula sheet, in which two cysteine residues (C) are bound by means of a sulphur bridge) of cfc1 was tested for 134 RA sera. This cyclic variant was shown to be reactive with 85 sera (63%), signifying an increase in sensitivity. Of the 151 sera of patients suffering from rheumatic diseases other than RA, 3 were shown to be positive (specificity 98%). The priority document of the present application reports 5

falsely determined positives. However, it has been shown that in two of these cases the patients did indeed suffer from RA. Not one serum from 59 healthy individuals was positive with this cyclic peptide, nor with any of the peptides cfc1 to cfc9. The cyclic peptide variant was shown to be reactive with 4 sera of the 200 additional control sera (50 SLE, 50 SCC, 50 pSS, 50 PM/DM) so that the specificity in respect of these sera was 98%. Of the sera from patients suffering from various infectious diseases (308 sera as described above), 7 sera were shown to be positive with the cyclic peptide variant so that in this case also the specificity in respect of these sera was 98%. The use of the cyclic peptide variant thus enhances the sensitivity compared with the individual linear peptide variants, but the specificity is also enhanced due to an improved signal/noise ratio in the described ELISA test.

A second citrulline-substituted peptide (nfc1) was shown to be specifically reactive with 10% of the RA sera, but not with the control peptide nf, which does not comprise citrulline. Of the RA sera reactive with nfc1, some were not reactive with cfc1 to cfc9. Therefore, it is possible to increase the sensitivity of a test for rheumatoid arthritis by applying more peptides comprising a modified arginine residue.

Obviously, a peptide may comprise several modified arginine residues, but the peptide may also comprise one or more non-modified arginine residues.

Applicants believe that modified amino acids, in particular those derived from arginine residues, could possibly also play a role in other autoimmune diseases. For this reason, the invention is also aimed at peptides comprising modified amino acids that are reactive with auto-antibodies from patients suffering from autoimmune diseases other than RA. This relates especially to peptides comprising a modified arginine residue wherein X = $NHCH_3$ (wherein Y = NH or NCH_3) or $NH(CH_3)_2$ is, which peptides will be useful for the detection of autoimmune diseases such as SLE, scleroderma, primary Sjögren's syn-

drome and polymyositis/dermatomyositis, in which nuclear autoantigens play a role. Said peptides are useful for the development of monoclonal antibodies against these diseases as well as for diagnosing the respective autoimmune diseases, in particular for the detection of autoimmune antibodies in body fluid such as blood, plasma and serum of patients who are suspected of suffering from the autoimmune disease. Again the peptides and antibodies offer the possibility of developing an organic compound with the aid of combinatorial chemistry, which compound is comprised within the scope of the invention.

The recombinant monoclonal antibody described by applicants is reactive with peptide cfc1 but not with the control peptides cfA, cfE, cfQ or cf. The commercially available monoclonal antibody AKH1 (Ref. 5), directed against human filaggrin, is not reactive with any of the peptides described herein and is therefore not cross-reactive with an antibody raised against a peptide according to the invention. The polyclonal serum anti-54 kD (Ref. 5), raised against filaggrin, is not reactive with any of the peptides described herein and is therefore not cross-reactive with an antibody reactive with a peptide according to the invention. This suggests that in a normal immune reaction antibodies that are cross-reactive with an antibody raised against a peptide according to the invention, are not necessarily formed.

REFERENCES

1) Smolen, J.S., (1996) Autoantibodies in rheumatoid arthritis, in Manual of biological markers of disease (W.J. van Venrooij and R.N. Maini, red.) Vol. C Chapter 1.1 pp. 1-18. Kluwer Scientific Publishers, Dordrecht.

2) McKinley-Grant, L.J., Idler, W.W., Bernstein, I.A., Parry, D.A.D., Cannizzaro, L., Croce, C.M., Huebner, K., Lessin, S.R. & Steinert, P.M. (1989) Characterization of a cDNA clone encoding human filaggrin and localization of the gene to chromosome region 1q21. Proceedings of the National Academy of Science U.S.A. 86, pp. 4848-4852.

3) Gan, S.Q., McBride, O.W., Idler, W.W., Nedialka, M. & Steinert, P.M. (1990) Organization, structure, and polymorphisms of the human profilaggrin gene. Biochemistry 29, pp. 9432-9440.

4) Schellekens, G.A., Lasonder, E., Feijlbrief, M., Kocdijk, D.G.A.M., Drijfhout, J.W., Scheffer, A.J., Welling-Wester, S & Welling, G.W. (1994) Identification of the core residues of the epitope of a monoclonal antibody raised against glycoprotein D of herpes simplex virus 1 by screening of a random peptide library. The European Journal of Immunology 24, pp. 3188-3193.

5) Hoet, R.M.A., Boerbooms, A.A.Th., Arends, M., Ruiter, D.J., van Venrooij, W.J. (1991) Antiperinuclear factor, a marker autoantibody for rheumatoid arthritis: colocalisation of the perinuclear factor and profilaggrin. Annals of the Rheumatic diseases 50, pp. 611-618.

CLAIMS

1. A peptide derived from an antigen recognized by autoantibodies from patients with rheumatoid arthritis, which peptide is reactive with autoimmune antibodies from a patient suffering from rheumatoid arthritis, characterized in that the derived peptide that is reactive with autoimmune antibodies, corresponds to a part of a mRNA molecule coding for the antigen, said part comprising a codon for an arginine residue, and the arginine residue in the derived peptide, which is reactive with autoimmune antibodies, is a modified arginine residue.

2. A peptide according to claim 1, characterized in that the modified arginine residue's side chain is a side chain according to Formula I on the formula sheet, in which

X = NH_2, CH_3, $NHCH_3$ or $N(CH_3)_2$;

Y = O, NH, $NHCH_3$ or $N(CH_3)_2$;

Z = O, NH or CH_2; and

n = 2, 3 or 4, on the condition that when X = NH_2 and Z = NH, Y is not NH.

3. A peptide according to claim 1 or 2, characterized in that the modified arginine residue is a citrulline residue.

4. A peptide according to one of the preceding claims, characterized in that the peptide is selected from the group of peptides having the Formula II - X.

5. A peptide according to one of the claims 1 to 3, characterized in that the peptide is a cyclic peptide.

6. A peptide according to claim 5, characterized in that the cyclic peptide is having the Formula XI.

7. A peptide according to one of the preceding claims, characterized in that the peptide is a synthetic peptide.

8. A peptide according to one of the preceding claims, characterized in that the antigen is (pro)filaggrin, and the peptide is reactive with a rheumatoid arthritis

patient's autoimmune antibodies which are reactive with (pro)filaggrin.

9. A peptide according to one of the claims 1 to 3, **characterized** in that the peptide is obtained by the proteolytic treatment of (pro)filaggrin, separation of peptide fragments formed by proteolysis and subsequent selection on the presence of a modified arginine residue in a peptide which was formed during the proteolytic treatment.

10. An antibody which is cross reactive with an antibody raised against a peptide according to one of the claims 1 to 9.

11. An antibody according to claim 10, **characterized** in that the antibody is a monoclonal antibody.

12. An antibody according to claim 10 or 11, **characterized** in that the antibody is obtained by using a peptide according to one of the claims 1 to 9 as an antigen.

13. An antibody according to one of the claims 9 to 12, **characterized** in that it is cross-reactive with the antibody as produced by Escherichia coli TG1 with plasmid RA3, deposited at the Centraalbureau voor Schimmelcultures, at Baarn, the Netherlands under accession number CBS143.96.

14. An organic compound comprising a part that is able to compete with a peptide according to one of the claims 1 to 9 for binding to an antibody which is specific for said peptide, wherein at least said part of the organic compound can be prepared by means of combinationary chemistry.

15. A method for the detection of autoimmune antibodies, **characterized** in that in an immunological test at least one immunologically reactive molecule selected from the group consisting of i) a peptide according to one of the claims 1 to 9; ii) an organic compound according to claim 14; and iii) an antibody according to one of the claims 10 to 13 is used.

I hereby certify that this paper is being deposited with the United States Postal Service on **May 13, 1999**, in an envelope as "Express Mail Post Office to Addressee" mailing Label No. **EL270182671US** addressed to Box PCT, Assistant Commissioner for Patents, Washington, D.C. 20231.

Annette M. Turk, Legal Assistant

May 13, 1999
(Date)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Waltherus J.W. Van Venrooij, Gerardus Antonius Schellekens, Jozef Maria Hendrik Raats,and Rene Michael Antonius Hoet

Serial No.: UNKNOWN

Examiner: UNKNOWN

Priority claimed to PCT/NL97/00624

Filed: Herewith (May 13, 1999)

Group Art Unit: UNKNOWN

For: PEPTIDE DERIVED FROM AN ANTIGEN RECOGNIZED BY AUTOANTIBODIES FROM PATIENTS WITH RHEUMATOID ARTHRITIS, ANTIBODY DIRECTED AGAINST SAID PEPTIDE, A COMBINATORIAL ANTIGEN, AND A METHOD OF DETECTING AUTO-IMMUNE ANTIBODIES

FIRST PRELIMINARY AMENDMENT

Box: PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend the application, without prejudice, as follows:

In the Claims:

1. (Amended) A peptide derived from an antigen recognized by autoantibodies from patients with rheumatoid arthritis, which peptide is reactive with autoimmune antibodies from a patient suffering from rheumatoid arthritis, [characterized in that] wherein the derived peptide that is reactive with autoimmune antibodies[,] corresponds to a part of a RNA molecule coding for the antigen, said part comprising a codon for an arginine residue, and the arginine residue in the derived peptide, which is reactive with autoimmune antibodies, is a modified arginine residue.

2. (Amended) A peptide according to claim 1 [, characterized in that] wherein the modified arginine residue's side chain is a side chain according to Formula I on the formula sheet, in which

$X = NH_2$, CH_3, $NHCH_3$ or $N(CH_3)_2$;

$Y = O$, NH, $NHCH_3$ or $N(CH_3)_2$;

$Z = O$, NH or CH_2; and

$n = 2$, 3 or 4, on the condition that when $X = NH_3$ and $Z = NH$, Y is not NH.

3. (Amended) A peptide according to claim 1 [or 2, characterized in that] wherein the modified arginine residue is a citrulline residue.

4. (Amended) A peptide according to [any one of the preceding claims, characterized in that] claim 1 wherein the peptide is selected from the group of peptides having the Formula II – X.

5. (Amended) A peptide according to [one of the claims 1 to 3, characterized in that] claim 1 wherein the peptide is a cyclic peptide.

6. (Amended) A peptide according to claim 5 [, characterized in that] wherein the cyclic peptide [is having] has the Formula XI.

7. (Amended) A peptide according to [one of the preceding claims, characterized in that] claim 1 wherein the peptide is a synthetic peptide.

8. (Amended) A peptide according to [one of the preceding claims, characterized in that] claim 1 wherein the antigen is (pro)filaggrin, and the peptide is reactive with a rheumatoid arthritis patient's autoimmune antibodies which are reactive with (pro)filaggrin.

9. (Amended) A peptide acording to [one of the claims 1 to 3, characterized in that] claim 1 wherein the peptide is obtained by the proteolytic treatment of (pro)filaggrin, separation of peptide fragments formed by proteolysis and subsequent selection of the presence of a modified arginine residue in a peptide which was formed during the proteolytic treatment.

10. (Amended) An antibody which is cross reactive with an antibody raised against a peptide according to [one of the claims 1 to 9] claim 1.

11. (Amended) An antibody according to claim 10 [, characterized in that] wherein the antibody is a monoclonal antibody.

12. (Amended) An antibody according to claim 10 [or 11, characterized in that] wherein the antibody is obtained by using a peptide according to [one of the claims 1 to 9] claim 1 as an antigen.

13. (Amended) An antibody according to [one of the claims 9 to 12, characterized in that] claim 9 wherein it is cross-reactive with the antibody as produced by *Escherichi coli* TG1 with plasmic RA3, deposited at the Centraalbureau voor schimmelcultures, at Baarn, the Netherlands under accession number CBS143.96.

14. (Amended) An organic compound comprising a part that is able to compete with a peptide according to [one of the claims 1 to 9] claim 1 for binding to an antibody which is specific for said peptide, wherein at least said part of the organic compound can be prepared by means of combinationary chemistry.

15. (Amended) A method for the detection of autoimmune antibodies [, characterized in that] wherein in an immunological test at least one immunologically reactive molecule selected from the group consisting of i) a peptide according to [one of the claims 1 to 9] claim 1; ii) an organic compound according to claim 14; and iii) an antibody according to [one of the claims 10 to 13] claim 10 is used.

REMARKS

The foregoing amendment is being offered in a format acceptable to the U.S. Patent and Trademark Office. Entry of this amendment by the Examiner is respectfully requested.

Authorization is given to charge payment of any fees required, or credit any overpayment, to Deposit Acct. 13-4213. A duplicate of this paper is enclosed for accounting purposes.

Respectfully submitted,

Dated: May 13, 1999

By: _____
Jeffrey D. Myers, Reg. No. 35,964
Direct line: (505) 998-1502

PEACOCK, MYERS & ADAMS, P.C.
Attorneys for Applicant(s)
P.O. BOX 26927
Albuquerque, New Mexico 87125-6927

Telephone: (505) 998-1500
Facsimile: (505) 243-2542

[\\JDM\DOCS\AMDS\Los&Stig\VanVenrooij.PAM.doc] 30394-1027

PATENT APPLICATION

I hereby certify that this paper is being deposited with the United States Postal Service on **May 13, 1999**, in an envelope as "Express Mail Post Office to Addressee" mailing Label No. **EL270182671US** addressed to Box PCT, Assistant Commissioner for Patents, Washington, D.C. 20231.

Annette M. Turk, Legal Assistant

May 13, 1999
(Date)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Waltherus J.W. Van Venrooij, Gerardus Antonius Schellekens, Jozef Maria Hendrik Raats,and Rene Michael Antonius Hoet

Serial No.: UNKNOWN

Examiner: UNKNOWN

Priority claimed to PCT/NL97/00624

Filed: Herewith (May 13, 1999)

Group Art Unit: UNKNOWN

For: PEPTIDE DERIVED FROM AN ANTIGEN RECOGNIZED BY AUTOANTIBODIES FROM PATIENTS WITH RHEUMATOID ARTHRITIS, ANTIBODY DIRECTED AGAINST SAID PEPTIDE, A COMBINATORIAL ANTIGEN, AND A METHOD OF DETECTING AUTO-IMMUNE ANTIBODIES

FIRST PRELIMINARY AMENDMENT

Box: PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend the application, without prejudice, as follows:

In the Claims:

1. (Amended) A peptide derived from an antigen recognized by autoantibodies from patients with rheumatoid arthritis, which peptide is reactive with autoimmune antibodies from a patient suffering from rheumatoid arthritis, [characterized in that] wherein the derived peptide that is reactive with autoimmune antibodies[,] corresponds to a part of a RNA molecule coding for the antigen, said part comprising a codon for an arginine residue, and the arginine residue in the derived peptide, which is reactive with autoimmune antibodies, is a modified arginine residue.

2. (Amended) A peptide according to claim 1 [, characterized in that] wherein the modified arginine residue's side chain is a side chain according to Formula I on the formula sheet, in which

$X = NH_2$, CH_3, $NHCH_3$ or $N(CH_3)_2$;

$Y = O$, NH, $NHCH_3$ or $N(CH_3)_2$;

$Z = O$, NH or CH_2; and

$n = 2$, 3 or 4, on the condition that when $X = NH_3$ and $Z = NH$, Y is not NH.

3. (Amended) A peptide according to claim 1 [or 2, characterized in that] wherein the modified arginine residue is a citrulline residue.

4. (Amended) A peptide according to [any one of the preceding claims, characterized in that] claim 1 wherein the peptide is selected from the group of peptides having the Formula II – X.

5. (Amended) A peptide according to [one of the claims 1 to 3, characterized in that] claim 1 wherein the peptide is a cyclic peptide.

6. (Amended) A peptide according to claim 5 [, characterized in that] wherein the cyclic peptide [is having] has the Formula XI.

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8. (Amended) A peptide according to [one of the preceding claims, characterized in that] claim 1 wherein the antigen is (pro)filaggrin, and the peptide is reactive with a rheumatoid arthritis patient's autoimmune antibodies which are reactive with (pro)filaggrin.

9. (Amended) A peptide acording to [one of the claims 1 to 3, characterized in that] claim 1 wherein the peptide is obtained by the proteolytic treatment of (pro)filaggrin, separation of peptide fragments formed by proteolysis and subsequent selection of the presence of a modified arginine residue in a peptide which was formed during the proteolytic treatment.

10. (Amended) An antibody which is cross reactive with an antibody raised against a peptide according to [one of the claims 1 to 9] claim 1.

11. (Amended) An antibody according to claim 10 [, characterized in that] wherein the antibody is a monoclonal antibody.

12. (Amended) An antibody according to claim 10 [or 11, characterized in that] wherein the antibody is obtained by using a peptide according to [one of the claims 1 to 9] claim 1 as an antigen.

13. (Amended) An antibody according to [one of the claims 9 to 12, characterized in that] claim 9 wherein it is cross-reactive with the antibody as produced by *Escherichi coli* TG1 with plasmic RA3, deposited at the Centraalbureau voor schimmelcultures, at Baarn, the Netherlands under accession number CBS143.96.

14. (Amended) An organic compound comprising a part that is able to compete with a peptide according to [one of the claims 1 to 9] claim 1 for binding to an antibody which is specific for said peptide, wherein at least said part of the organic compound can be prepared by means of combinationary chemistry.

15. (Amended) A method for the detection of autoimmune antibodies [, characterized in that] wherein in an immunological test at least one immunologically reactive molecule selected from the group consisting of i) a peptide according to [one of the claims 1 to 9] claim 1; ii) an organic compound according to claim 14; and iii) an antibody according to [one of the claims 10 to 13] claim 10 is used.

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Direct line: (505) 998-1502

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Attorneys for Applicant(s)
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Albuquerque, New Mexico 87125-6927

Telephone: (505) 998-1500
Facsimile: (505) 243-2542

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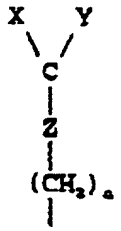
FORMULA SHEET

I 

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VIII S H Q E S T X G R S X G R S G R S G S

IX S H Q E S T X G R S R G X S G R S G S

X S H Q E S T X G R S R G R S G X S G S

XI H Q C H Q E S T X G R S R G R C G R S G S

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Applicants: Waltherus J.W. Van Venrooij, Gerardus Antonius Schellekens, Jozef Maria Hendrik Raats,and Rene Michael Antonius Hoet

Serial No.: UNKNOWN

Examiner: UNKNOWN

Priority claimed to PCT/NL97/00624

Filed: Herewith (May 13, 1999)

Group Art Unit: UNKNOWN

For: PEPTIDE DERIVED FROM AN ANTIGEN RECOGNIZED BY AUTOANTIBODIES FROM PATIENTS WITH RHEUMATOID ARTHRITIS, ANTIBODY DIRECTED AGAINST SAID PEPTIDE, A COMBINATORIAL ANTIGEN, AND A METHOD OF DETECTING AUTO-IMMUNE ANTIBODIES

ASSOCIATE POWER OF ATTORNEY

Box: PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Jeffrey D. Myers, a principal attorney in the above-identified application for Letters Patent, hereby

appoints: Deborah A. Peacock, Reg. No. 31,649
Paul Adams, Reg. No. 21,096
Rod D. Baker, Reg. No. 35,434
Brian J. Pangrle, Reg. No. 42,973
Nancy E. Ownbey, Reg. No. 38,986;
Andrea L. Mays, Reg. No. 43,721; and
Stephen A. Slusher, Reg. No. 43,924

as associate attorneys with full power.

Respectfully submitted,

Date: 13 May 1999

Jeffrey D. Myers, Reg. No. 35,964
Direct line: (505) 998-1502

Attorney for Applicant(s)
PEACOCK, MYERS & ADAMS, P.C.
P.O. Box 26927
Albuquerque, New Mexico 87125-6927
Telephone: (505) 998-1500
Facsimile No. (505) 243-2542
Customer No. 005179

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	30394-1027
First Named Inventor	Van Venrooij
COMPLETE IF KNOWN	
Application Number	09 / 308,150
Filing Date	13 May 1999
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PEPTIDE DERIVED FROM AN ANTIGEN RECOGNIZED BY AUTOANTIBODIES FROM PATIENTS WITH RHEUMATOID ARTHRITIS, ANTIBODY DIRECTED AGAINST SAID PEPTIDE, A COMBINATORIAL ANTIGEN AND A METHOD OF DETECTING AUTO-IMMUNE ANTIBODIES

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☒ was filed on (MM/DD/YYYY) November 14 1997 as United States Application Number or PCT International Application Number PCT/NL97/00624 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
PCT/NL97/00624	Netherlands		☐	☐	☒
NL 1004539			☐	☐	☒
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
		☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

Burden Hour Statement: This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

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Attorney Docket Number	30394-1027
First Named Inventor	Van Venrooij
COMPLETE IF KNOWN	
Application Number	09 / 308,150
Filing Date	13 May 1999
Group Art Unit	
Examiner Name	

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PEPTIDE DERIVED FROM AN ANTIGEN RECOGNIZED BY AUTOANTIBODIES FROM PATIENTS WITH RHEUMATOID ARTHRITIS, ANTIBODY DIRECTED AGAINST SAID PEPTIDE, A COMBINATORIAL ANTIGEN AND A METHOD OF DETECTING AUTO-IMMUNE ANTIBODIES

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☒ was filed on (MM/DD/YYYY) November 14 1997 as United States Application Number or PCT International Application Number PCT/NL97/00624 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

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I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
PCT/NL97/00624			☐	☐	☒
NL 1004539	Netherlands		☐	☐	☒
			☐	☐	☐
			☐	☐	☐

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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☒ Customer Number 005179 → *Place Customer Number Bar Code Label here*
OR
☒ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number
Jeffrey D. Myers	35,964		

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☒ Customer Number or Bar Code Label 005179 *OR* ☒ Correspondence address below

Name	Jeffrey D. Myers				
Address	PEACOCK, MYERS & ADAMS				
Address	Post Office Box 26927				
City	Albuquerque	State	NM	ZIP	87125-6927
Country	US	Telephone	(505) 998-1500	Fax	(505) 243-2542

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
WALTHERUS JACOBUS WILHELMUS	VAN VENROOIJ

Inventor's Signature						Date	June 24 1999
Residence: City	Nijmegen	State		Country	Netherlands	Citizenship	Dutch
Post Office Address	Eleonoraweg 16						NLX
Post Office Address	NL-6523 XV						
City	Nigmegen	State		ZIP		Country	Netherlands

☒ Additional inventors are being named on the ____ supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

Please type a plus sign (+) inside this box → [+]

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DECLARATION

ADDITIONAL INVENTOR(S) Supplemental Sheet
Page 1 of 1

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
GERARDUS ANTONIUS			SCHELLEKENS				
Inventor's Signature					Date		
Residence: City	Nijmegen	State		Country	Netherlands	Citizenship	Dutch
Post Office Address	Zwanenveld 37-03						
Post Office Address	NL-6538 XV						
City	Nijmegen	State		ZIP		Country	Netherlands

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
JOZEF MARIA HENDRIK			RAATS				
Inventor's Signature					Date	June 24 1994	
Residence: City	Nijmegen	State		Country	Netherlands	Citizenship	Dutch
Post Office Address	Van Diemerbroeckstraat 65 NLX						
Post Office Address	NL-6512 BA						
City	Nijmegen	State		ZIP		Country	Netherlands

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
RENE MICHAEL ANTONIUS			HOET				
Inventor's Signature					Date	June 24 1999	
Residence: City	Nijmegen	State		Country	Netherlands	Citizenship	Dutch
Post Office Address	Weezenhof 35 - 40 NLX						
Post Office Address	NL 6536 HB						
City	Nijmegen	State		ZIP		Country	Netherlands

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Post Office Address	NL-6512 BA						
City	Nijmegen	State		ZIP		Country	Netherlands
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